REMARKS

Status

The Applicants have amended the specification to add a brief description of the drawings as requested by the Examiner.

The Applicants have cancelled claims 2, 3 and 5-13 and have replaced them with new claims 14-26. The intent is to re-order the claims in response to the Examiner's objection to the numbering of the prior claims. Reexamination is respectfully requested.

Objections to the Specification

The Examiner acknowledged the Applicants' submission of copies of Figures 1-6, but continued to object to the specification. The Examiner stated that a brief description of the drawings (figures) is required.

The Applicants have amended the specification to provide such a description.

Objections to the Claims

Examiner objected to claims 2, 3 and 5-9 as improper dependent claims because they did not refer back to or depend on a preceding claim.

In response, the Applicants have provided new claims 14-24. New claim 14 is now the independent claim and replaces prior claim 10. New claims 15-24 replace prior claims 2, 3, 11, 12, 13, 5, 6, 7, 8, and 9 respectively. New claims 25 and 26 were added to further define the invention.

Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected the pending claims under Section 112, second paragraph, as indefinite for allegedly omitting essential steps, citing MPEP §2172.01. Similarly, the Examiner

asserted that claim 10 was unclear because the transgene expression could not take place in the absence of an operably linked promoter.

The Applicants respectfully traverse the rejection. The allegedly omitted steps and promoter are well-known to those skilled in the art and are not necessary or essential elements of the invention. MPEP §2171.01, second paragraph, states that "[A] claim which fails to interrelate **essential elements of the invention as defined by applicant(s) in the specification** may be rejected under 35 U.S.C. 112, second paragraph...." (Emphasis added.) The specification does not define the steps referenced by the Examiner as essential elements of the invention. Nevertheless, in order to advance the prosecution, the Applicants have submitted new claim 14, which specifies certain additional steps, known to those skilled in the art, involved in the production of transgenic animals. Please see the enclosed copies of chapters 6 and 7 from DNA Cloning 4: A Practical Approach, edited by D.M. Glover and B.D. Hames, Oxford University Press, 1995.

Therefore, the Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

Rejection Under 35 U.S.C. §112 – Written Description

Examiner rejected the claims on the grounds that they did not meet the written description requirements of §112, first paragraph. The Examiner asserted that the written description did not support a claimed genus that included all mammals and parts of nectin-1 as well as the extracellular domain.

The Applicants respectfully traverse the rejection. However, in order to advance the prosecution, and without forsaking their right to pursue broader claims in a continuation application, the Applicants have amended the claims to be directed to mammals selected from the group consisting of mice, pigs, and cattle and to be directed to the VCC and V domains of nectin-1. The VCC domain is the extracellular domain of nectin-1, and the V domain is a

portion thereof. Use of the V domain is shown in example 4, and described on page 23 of the specification.

The description supports the newly claimed genus. The examples show that the transgenic animals and cells that express the modified receptor for the virus are resistant to infection by the virus. Moreover, the polypeptide sequence of nectin-1 is remarkably well conserved between the mouse, porcine and bovine species of mammals, which provides a reasonable basis for assuming a significant structural and functional identity between the chimeric proteins in these species. Please see table 1 on page 317 of the enclosed copy of Milne, *et al.*, "Porcine HveC, a Member of the Highly Conserved HveC/Nectin-1 family, is a Functional Alphaherpesvirus Receptor, Virology, 281, 315-328 (2001). Table 1 shows a 97% amino acid identity of the HveC extracellular domains for pigs and cows, and it shows a 93% identity between mice and pigs and cows.

Therefore, in view of the amendments to the claims and the remarks, the Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

Rejection Under 35 U.S.C. §112 – Enablement

The Examiner rejected the pending claims under §112, first paragraph, for a lack of enablement. The Examiner asserted: (1) the specification does not provide an enabling disclosure for the production of the numerous species of transgenic mammals within the scope of the claims; (2) the specification does not provide an enabling disclosure for the generation of transgenic mammals by homologous recombination; and (3) the specification does not provide an enabling disclosure for the production of mammals expressing fusion proteins of nectin-1 or its parts. Moreover, the Examiner asserted that: (1) the data suggest that the route of infection likely plays a role in the degree of resistance to viral infection; (2) resistance appears dependent on both the type of receptor and the particular virus; and (3) a given construct may act differently from one species to another. The Examiner further stated that there is no description of how parts of nectin-1 may be used in the chimeric protein.

The Applicants respectfully traverse the rejection. The amended claims are now limited to pigs, cattle and mice and to chimeric proteins including the VCC or V domains of porcine or bovine nectin-1. In addition, nuclear transfer gene introduction by homologous recombination is extensively documented in mice (Wakayama, et al., "Full-Term Development of Mice from Enucleated Oocytes Injected with Cumulus Cell Nuclei," Nature 394, 369 - 374 (23 Jul 1998); in sheep (Denning, et al., "Deletion of the α(1,3)Galactosyl Transferase (GGTA1) Gene and the Prion Protein (PrP) Gene in Sheep," Nature Biotechnology 19, 559 - 562 (01 Jun 2001); and in pigs (Dai, et al,"Targeted Disruption of the α1,3-Galactosyltransferase Gene in Cloned Pigs," Nature Biotechnology 20, 251-255 (March 2002). See also Forsberg, *et al.*, "Production of Cloned Cattle from In Vitro Systems," Biology of Reproduction 67, 327-333 (2002); Kasinathan, *et al.*, "Production of Calves from G1 Fibroblasts," Nature Biotechnology 19, 1176-1178 (December 2001); and Enright, *et al.*, "Reproductive Characteristics of Coned Heifers Derived from Adult Somatic Cells," Biology of Reproduction 66, 291-296 (2002). Copies of these articles are enclosed.

The Examiner cited data presented in the specification, relating to viral challenges of HveM-Ig transgenic mice (page 5, fourth paragraph), as examples of unpredictable results for the claimed process and transgenic animals. Applicants, however, respectfully point that, as detailed in the references cited in the specification, HveM (or HveA) and HveC (or nectin-1) are largely different proteins. In this context, and more specifically, HveM is a known receptor of HSV (Herpes Simplex virus) but not a receptor for PRV (pseudorabies virus). HveC, or nectin-1, on an other hand, is a known receptor of both HSV and PRV viruses. Considering that background information, the lack of resistance to PRV infection of HveM-Ig transgenic mice, actually supports the logical link between expressing a soluble and disabled form of a viral receptor and enhancing resistance to a virus using this specific receptor.

The Examiner further noted that challenge results are different according to the route of infection for HveC-Ig transgenic mice challenged with PRV. This is generally expected from such challenge experiments that use transgenic or control animals, as different routes of infection translate into different pathogenesis and clinical syndromes. Specifically, intranasal challenges

makes possible direct viral replication of viruses from nose epithelium to CNS cells, leading quickly to encephalitis. However, the intranasal route is typically relevant to targeted pig pathogenesis, where natural infection occurs by nasal and oral routes. Infection via intraperitoneal injections is expected to result similar results to infection by intravenous injections, and is usually preferred in mice for reasons of convenience and repeatability. Regarding a model of PRV infection in pigs, intranasal challenge is clearly more appropriate than intravenous challenge.

Results for intranasal challenge are effectively reduced compared to intraperitoneal challenges; however, they are still very impressive (70% survival) in such a lethal test.

An in vivo infection test was performed on growing pigs from HveC(VCC-Fc) pig transgenic lines, described in our previous reply, compared to control pigs at the age of 5 months: 6 transgenic pigs and 6 controls were challenged intranasally and orally with 106 PFU.PRV/Kojnock virus strain per pig. Growth was recorded weekly for each pig after infection as infection is not lethal in pigs at this stage and is the criteria used to qualify efficiency of vaccines used for pigs.

	Transgenic pigs HveC(VCC-Fc)	Control pigs
Weight at challenge Day 0	87.9 kg	89.4 kg
Daily gain Day 0 to Day 7	-265 g	-1035 g
Daily gain Day 7 to Day 13	1806 g	606 g
Daily gain Day 13 to Day 19	1446 g	1036
Daily gain Day 0 to Day 19	**961 g**	**130 g**

Trangenic HveC(VCC)-Fc pigs gained 0.8 kg/day more than control pigs during challenge time period. Transgenic pigs showed a very significant protection in this viral challenge, comparable to the usual efficiency of sub-unit vaccines used in the field to control the disease.

Therefore, the Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

Rejection Under 35 U.S.C. §103

The Examiner continued to reject the claims under Section 103(a) as obvious in view of Fiume, *et al.* considered with Bujard, *et al.* The Examiner cited Bujard, *et al.* for disclosing the production of transgenic animals, such as mice, expressing a chimeric protein. The Examiner asserted that Fiume, *et al.* describes various fusion proteins between segments of HIgR (herpesvirus immunoglobulin-like receptor) and the Fc of human IgG1. The Examiner further asserted that an object of the Fiume, *et al.* invention is to provide cells that are resistant to infection by HSV-1, HSV-2, and BHV-1. The Examiner also mentioned that the combined teachings of Ono, *et al.*, cited by the Applicants, and Bujard, *et al.* render obvious the application of the invention to transgenic mice.

The Applicants respectfully traverse the rejection. Turning first to the Ono, *et al.* reference, the Applicants point out that its publication date, November 16, 2004, is after both the priority date of the application, October 15, 2002, and its international filing date, October 14, 2003. Therefore, it cannot be prior art to the claimed invention.

As to the Fiume, *et al.* reference, the Applicants submit that it discloses the use of nectin-1 for an entirely different purpose than its use in the claimed invention. Therefore, the reference teaches away from the claimed invention and cannot , in combination with Bujard, *et al.*, render the claimed invention obvious.

Fiume, *et al.* mentions "cells resistant to infection by HSV-1, HSV-2 and BHV-1" (column 1, line 66) only for the purpose of "biotechnological identification and production of proteins which act as mediators of HSV in human or animal models." (See col. 1, lines 66-67. Emphasis added.) This is further detailed in column 2, lines 47-53, which state that "the screening of a human expression library for ones that restored susceptibility to J1.1-2 cells led to the isolation of ..." (emphasis added), which is, in fact, selecting a molecule that, when added to such resistant cells, restores infection susceptibility. (The complete method is described in column 7, lines 43-67, and column 8, lines 1-4.) The resistant cells are then cited as an example of a discovery path for claimed methods, all related to the role of the HIgR/HveC/nectin-1 viral

receptor. More specifically, the "resistant cells" cited in Fiume, et al. have not acquired resistance through the introduction or use of the HveC molecule. Instead, their essential property and use is to acquire or restore susceptibility following a second step, which is the introduction of a viral receptor such as HveC. Therefore, a person skilled in the art would then not have been able to envision -- based on the disclosure of these cells, which are resistant to HSV, but devoid of the expression of HveC/nectin-1/HIgR molecules -- that transgenic animals expressing extracellular domains of HveC would become resistant to alphaherpes virus infection.

The Examiner also stated that Fiume, et al. mentions "transgenic mice expressing HIgR or HIgR and PRR-2, or HIgR and other mediators of HSV-1, HSV-2 and BHV-1 entry" (column 3, lines 15-17 and lines 46-48), but did not say that these animals would be expected to be resistant to herpesvirus infection. In fact, the same paragraphs later discloses certain applications envisioned for these transgenic animals. These applications entail "efficacy studies of antiherpes virus drugs, antiherpes antibodies..." (lines19-21) or "a mouse model that sustains BHV-1 infection", to be used for testing therapeutic compounds or vaccines. (See column 3, lines 50-51. Emphasis added.) The same transgenic mice are also referred to in column 3, lines 25 -28 as useful for establishing a mouse model for efficacy studies of herpes simplex viral vectors against CNS tumors. The usefulness of such animal models clearly implies that the transgenic animals are supposed to be susceptible to such infections.

The two next paragraphs (column 3, lines 30-44) disclose new uses of the same transgenic mice, susceptible to Herpes virus infections, and usable for "efficacy studies" of live vaccine strains of herpes virus (line 35) or "efficacy studies" of compounds that "interfere" with HSV latency and reactivation (line 44). Resistant mice would not make any sense in such a context.

The Examiner also stated that Fiume, et al. describes various fusion proteins between various segments of HIgR and the Fc portion of human IgG1. However, Fiume, et al. cites this form of Hvec as a demonstration of the gD binding properties of HveC, which is exemplified by Mab R1.302 epitope mapping detailed in Figure 7 of the same document. Therefore, the fusion

proteins were disclosed in a different context and for the purpose of demonstration. Considering that transgenic animals cited as applications by Fiume, et al. are those expressing the full-length receptor (and not the fusion proteins) for the purpose of increased virus susceptibility in various animal models, a person of ordinary skill in the art would not have imagined a totally different use as in the claimed invention.

In summary, Fiume, et al. clearly discloses transgenic mice expressing full length HIgR (or nectin-1) and, therefore, fully functional receptors for alphaherpes viruses. This is in direct contrast with the claimed invention, which relates to transgenic mammals expressing truncated forms of nectin-1 (e.g., the extracellular domain), which make it possible to inhibit virus entry when secreted or exposed on the cell membrane.

Therefore, the Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

Conclusion

Applicants believe that the present application is now in condition for allowance or in better form for appeal. Therefore, the Examiner is respectfully requested to enter the amendment and reconsider the application.

The Examiner is invited to contact the undersigned by telephone if it is believed that a telephone interview would advance the prosecution of the application.

Respectfully submitted,

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